Human Pathology (2017) **60**, 167–173

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Multivacuolated mucin-filled cells: a unique cell characteristic of plexiform neurofibroma. A report of 11 cases☆

Michael Michal MD[a,*], Dmitry V. Kazakov MD[b], Ladislav Hadravský MD[c], Květoslava Michalová MD[b], Boris Rychlý MD[d], Michal Michal MD[b]

[a]*Department of Pathology, Charles University, Biomedical Center, Faculty of Medicine in Plzen and Charles University Hospital Plzen, Alej Svobody 80, 304 60 Pilsen, Czech Republic*
[b]*Department of Pathology, Charles University, Medical Faculty and Charles University Hospital Plzen, Alej Svobody 80, 304 60 Pilsen, Czech Republic*
[c]*Department of Pathology, Charles University, Third Medical Faculty and Charles University Hospital Kralovske Vinohrady, Šrobárova 50, 100 34 Prague, Czech Republic*
[d]*Cytopathos, Limbová 5, 833 07, Bratislava 37, Slovakia*

Received 15 August 2016; revised 9 October 2016; accepted 14 October 2016

Keywords:
Soft tissue;
Plexiform neurofibroma;
Multivacuolated lipoblast-like cells;
Multivacuolated mucin-filled cells;
Perineurial cells

Summary The authors present 11 cases of plexiform neurofibroma (PN) that featured a very characteristic type of cell appearing as multivacuolated mucin-filled cells (MMFC). The 11 cases were obtained after reviewing 109 cases of PN. Six out of 10 patients showed clinical features of neurofibromatosis type 1. The size of PN ranged from 0.8 cm to 11.5 cm in the largest dimension. The lesions represented classical PN in all cases with myxoid, hypocellular stroma. The MMFC were found within the most myxoid tumorous nodules and were haphazardly located, typically featuring a variably sized, multivacuolated cytoplasm divided by fine septa with a small polygonal nucleus on one side, which was often compressed or slightly indented by the cytoplasmic mucous substances. In many cases, the cells resembled a soccer ball or a jellyfish. In all tested cases (n = 9), the MMFC stained for CD34; six cases were also positive with GLUT-1 antibody, and two cases expressed Claudin-1, whereas S-100 protein was negative. For comparison, we have reviewed a series of randomly selected non-PN, malignant peripheral nerve sheath tumors (MPNST) and of cases featuring non-neoplastic nerve trunks in our files, in which no MMFC were encountered. MMFC seem to be unique to myxoid areas of PN, where they occur in about 10% of cases. Their exact histogenesis is unclear but they might represent an intermediate type of cell between perineurial cells and fibroblasts. The awareness of this cell type in PN is especially important in limited (small) biopsy specimens where their recognition may provide a clue for the correct diagnosis.

☆ Ethics and Competing interests: The authors have no conflict of interest to disclose. When necessary, informed consent was obtained for experimentation with human subjects. This study was supported by the National Sustainability Program I (NPU I) Nr. LO1503 provided by the Ministry of Education Youth and Sports of the Czech Republic.

* Corresponding author: Department of Pathology, Charles University, Medical Faculty and Charles University Hospital Plzen, Alej Svobody 80, 304 60 Pilsen, Czech Republic.
E-mail address: michael.michal@medima.cz (M. Michal).

http://dx.doi.org/10.1016/j.humpath.2016.10.010
0046-8177/

1. Introduction

Neurofibroma is a benign peripheral nerve sheath tumor composed of a variable admixture of Schwann, perineurial-like, perineurial, mast and fibroblastic cells. Five neurofibroma subtypes are recognized, one of which is plexiform neurofibroma (PN) [1]. Its recognition is important since, according to some studies, as much as 85% of cases PNs are associated with neurofibromatosis type 1 (NF1) [2], and in addition, they are more prone to undergo a malignant transformation than the remaining four subtypes.

Recently, while reviewing a set of PN for other purposes, in a minority of the cases we have repeatedly encountered an unusual and highly distinctive type of cell, which appeared multivacuolated and mucin filled. This compelled us to review a larger series of PN in order to define the frequency of occurrence of these cells and to study their variations and immunoprofile. For comparison, we have reviewed a series of randomly selected non-PN, malignant peripheral nerve sheath tumors (MPNST) and of cases featuring non-neoplastic nerve trunks in our files to determine whether multivacuolated mucin-filled cells (MMFC) are unique to PN among all the neurofibromatous tumors.

We are presenting 11 cases of PN containing MMFC with an immunohistochemical (IHC) analysis and follow-up information. As far as we are aware, this type of cell in neurofibromas has not been described so far.

2. Materials and methods

The 11 cases of PN constituting the subject of this study were retrieved from the Pilsner consultation tumor registry and the routine biopsy archive; they came from the period between years 1993–2016. The clinical information was extracted from the registry records, and follow-up data obtained from attending clinicians. To retrieve these 11 cases, we searched our files using key words “plexiform neurofibroma”. This search yielded altogether 109 specimens (68 cases from the routine biopsy archive, 41 from the consultation registry), which were reviewed to confirm the diagnosis. MMFC were identified in 11 of the 109 cases. In all but 2 cases, paraffin blocks or unstained reserve slides were available for an immunohistochemical study. For conventional microscopy, tissues were fixed in formalin, routinely processed and stained. Alcian blue pH 2.5 staining was performed to highlight the intracellular mucin. The IHC features were analyzed using a Ventana BenchMark ULTRA (Ventana Medical Systems, Inc, Tucson, AZ). The primary antibodies employed are shown in the Table 1. They were visualized using the enzymes alkaline phosphatase or peroxidase as detecting systems (both purchased from Ventana Medical Systems, Inc).

3. Results

3.1. Clinical findings

The clinical features are summarized in Table 2. The patients were 9 women and 2 men. The age of the patients at the time of diagnosis ranged from 7 to 71 years (average, 21.7 years). Follow-up information was available for 10 patients, and 6 had clinical features of NF1. One patient developed a MPNST in another location (Table 2). The average duration of follow-up was 10.3 years (range, 1-17 years). The tumor size ranged from 0.8 cm to 11.5 cm in the largest dimension, with an average size of 3.4 cm.

3.2. Histopathological findings

In all cases, the histological appearance was very similar. The lesions represented classical PN, showing variably distended nerve fascicles in a plexiform arrangement with myxoid, hypocellular stroma composed of a typical admixture of Schwann cells, fibroblasts, mast cells and few perineurial cells along with intervening non-neoplastic nerve axons and collagen fibers. The MMFC were exclusively distributed within the most myxoid tumorous nodules among PNs (Fig. 1), where they were haphazardly or somewhat equidistantly located (Fig. 2). The cells typically featured a variably sized, multivacuolated cytoplasm divided by fine septa with a small polygonal nucleus that was dislodged to the periphery of the cells and was often compressed or slightly indented by the cytoplasmic mucous substance. In rare instances, the cells were binucleated. Often the cells resembled a soccer ball or a jellyfish (Fig. 3).

In Case 2, following the excision of the PN, the patient developed an MPNST in another location. After reviewing slides from all 33 block of the malignant lesion, we did not find any MMFC. In several cases, mature adipose tissue was present in the sections, showing no signs of lipoblastic differentiation.

In Case 1, 2 consecutive biopsies were available, both featuring PN with MLLCs. In Case 10, altogether five PN from various body sites were simultaneously excised from one patient, with 3 of them containing MMFC.

For comparison, we reviewed 30 randomly selected non-plexiform neurofibroma cases and 60 MPNST to determine if MMFC are unique to PN. Neither the non-PNs nor MPNST contained MMFC. We also reviewed 30 specimens from various conditions in which non-neoplastic nerve trunks were present. Similarly, none of the cases featured MMFC.

3.3. Histochemical and immunohistochemical findings

With the Alcian blue pH 2.5 stain, the vacuoles of MMFC showed positive staining, providing evidence that they contain mucus. In all nine cases with available blocks, the MMFC